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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,957	02/03/2005	Jonathan S. Stamler	STAM3002 PCT	6780

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,957	STAMLER ET AL.	
	Examiner	Art Unit	
	GiGi Huang	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The amendment filed January 9, 2008 has been received, entered and carefully considered. The amendment affects the instant application accordingly:

(A) Claims 1-74 have been cancelled.

(B) Claims 75-83 have been added.

2. Claims 75-83 are pending in the case.

3. Claims 75-83 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 75-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for *every* coronary syndrome and condition, restenosis, asthma, or rectal spasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in

In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to *every* unstable coronary condition, restenosis, asthma, and rectal spasms. Thus, the claims taken together with the specification imply the invention is capable of addressing each and every one of these conditions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art shows that nitroglycerin is currently advised for use in angina but the benefits with or congestive heart failure have not been established to date, and are contraindicated in acute myocardial infarction, constrictive pericarditis, and pericardial tamponade (see previous Physician Desk Reference pages). As taught by Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not

adequate initial therapy for asthmatic attacks, in fact he teaches that its use could be dangerous. Applicant submitted two journal abstracts: Rolla, G., et al., Pulmonary Pharmacology 1995, April - June, 8(2-3): 137-141 and Sharara, A.M., et al., Pulmonary Pharmacology and Therapeutics 11(1), 65-70 (February 1998), stating others found a benefit of nitroglycerin for asthma. The abstract by Rolla et al. is teaching the effect of nitroglycerin pretreatment for the effectiveness of the beta-agonists (e.g. salbutamol) and theophylline administered which are the treating agents in the abstract, not the nitroglycerin. The abstract by Sharara, A.M., et al. states that there is conflicting reports regarding the efficacy of GTN as a bronchodilator (second sentence of abstract). The study was on 18 patients and while bronchodilating effects were seen, the mechanism is not known, there is no indication as to why the results are different from those in Kennedy et al., especially as Sharara states that there are conflicting reports on the issue. This underscores the unpredictability of the drug for enablement for asthma and that there is no reasonable expectation for success to the degree that it is not currently recommended for treatment asthma (see previous PDR pages from 2006). The unpredictability for the drug in the art is high and it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug, resulting in an unclear expectation of what would be successful.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance solely for angina in Examples XXXII and XXXIII. However, the specification does not provide for all other unstable coronary condition, restenosis, asthma, and rectal spasms.

(8) The quantity of experimentation necessary:
Considering the state of the art as discussed by the references above, particularly with regards to the high degree of unpredictability in the art for nitroglycerin, it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug. Without experimentation, as currently claimed, the scope of the invention would require undue experimentation of one skilled in the art to address each and every condition and every combination without a clear expectation of success.

As evidenced therein, along with the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 75-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite as to the expression of "administering inactivated mtALDH activating effective amount of agent". It is unclear what the phrase is directed to. Such a phrase fails to clarify the scope that applicant seeks protection for. It does not clarify for one of skill in the art where the metes and bounds of the invention are.

For the purposes of examination, the administration of dihydrolipoic acid, dithiothreitol, or tris(2-carboxyethylphosphine) will be appropriate.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 75-78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

It is noted that the claims as written given its broadest reasonable interpretation is a patient who has received nitroglycerin therapy at some point in time as it does not designate that the patient is currently treated and when treated with nitroglycerin, a patient inherently has some degree of tolerance.

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance.

It is noted that the translation provided is a machine translation from the European Patent Office and for clarity "alpha Liposaure" is alpha-lipoic acid and "Glyceroltrinitrate" is nitroglycerin.

Weischer teaches the combination of alpha-lipoic acid (enantiomers, derivatives or metabolites) and organic nitrates, including nitroglycerin in combination preparation. He teaches that the combination showed a greater anti-ischemic effect than when the nitroglycerin was administered alone. Thereby the combination of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) showed a therapeutic anti-organic nitrate tolerance effect. There were in vitro and in vivo models performed.

The in vivo models were comprised of administering by balloon catheter to animals (dog and house pig) with follow up histological investigation. The combination is envisioned for angina pectoris, nitrate tolerance, among other conditions. Weischer teaches the composition and methods of administration for angina with humans.

The patients will inherently have some degree of tolerance as administration of nitroglycerin produces tolerance that increases over time and angina is a chronic condition (see DE 4420102, Page 6, Table 1). Administration of the combination to angina patients will inherently affect the mtALDH as the limiting step is administration of

alpha-lipoic acid/dihydrolipoic acid (dithiol). The process of affecting the mtALDH would inherently occur once administered to the patient.

It is noted that "[T]he discovery of a previously unappreciated property of a prior art composition, **or of a scientific explanation for the prior art's functioning**, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

An inherent feature need not be recognized at the time of the invention. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, **but only that the subject matter is in fact inherent in the prior art reference**. The fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.

Weischer goes on to claim the method of use in Claim 21 of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) for angina pectoris, nitrate tolerance, among other conditions (citations are based on the translation provided – Specification: Page 1, paragraphs 1, 7, 9, 16-17 of 19 on page, Page 2, paragraphs 2-9 of 18 on page, Page 4, paragraph 2-10 of 28 on page, Page 6, paragraph 10-14 of 21 on page, Page 7, paragraph 14 of23 on page, Claim set: Page 2, claim 21).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 75-77, 79, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weischer et al. (DE 4420 102 A1) in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation).

The teachings of Weischer et al. are addressed above.

Weischer et al. does not expressly teach the use dithiothreitol (DTT).

Prugin et al. teaches that dihydrolipoic acid is an effective thiol, especially as a reducing agent. It was tested along with dithiothreitol (DTT) and glutathione in the presence of thiol-alkylating agents. DTT and dihydrolipoic acid were able to reverse the inhibition of the alkylating agents with DTT reversing the inhibitory effects of all three alkylating agents and the dihydrolipoic acid reversing only one alkylating agent (ebselen). Glutathione however was not able to reverse the inhibitory effects.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize dithiothreitol (DTT), as suggested by Prugin, and produce the instant invention.

As DTT was able to reverse the inhibitory effects of all three alkylating agents and the dihydrolipoic acid was able to reverse only one alkylating agent (ebselen), it would have been obvious to one of skill in the art at the time of the invention to substitute DTT for dihydrolipoic acid as the effective reductant for the same capacity to combine with the nitroglycerin. Prugin taught that dihydrolipoic acid and DTT are effective thiols, especially as reducing agents. One of skill in the art at the time would utilize DTT as it has many reductant and protective properties, especially its in light of its ability to overcome inhibition in comparison to glutathione and dihydrolipoic acid.

One of ordinary skill in the art would have been motivated to do this because utilization of a more effective reductant such as would result in a more effective therapy and product which is always desirable.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

13. Claims 75-83 are rejected under 35 U.S.C. 103(a) as being unpatentable Weischer et al. (DE 4420 102 A1) in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation), and in view

of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry).

The teachings of Weischer et al. (DE 4420 102 A1) in view of Prugin et al. are discussed above.

Weischer et al. (DE 4420 102 A1) in view of Prugin et al. does not expressly teach the use of tris(2-carboxyethyl)phosphine.

Getz et al. teaches that the sulfydryl reductant tris(2-carboxyethyl)phosphine (TCEP) is an attractive alternative to commonly used dithiothreitol (DTT). The reductants preserve enzymatic activity that is sensitive to sulhydryl oxidation equally. However, TCEP is desirable because it is more stable than DTT especially for long-term storage wherein DTT would require metal chelates in the buffer for preservation.

TCEP is noncompetitive with protein sulfydryls for attachment of thiol-reactive dyes giving TCEP a major advantage over DTT. Getz concluded that TCEP had clear advantages over DTT, and thereby preferable, but the choice of reductant is application specific (Abstract, Page 73, 2nd column, Page 74, 1st column, Page 80).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute tris(2-carboxyethyl)phosphine for DTT, as suggested by Getz, and produce the instant invention. One of skill in the art at the time would utilize tris(2-carboxyethyl)phosphine as it has many advantages over DTT, especially its stability for testing, administration, and manufacture.

One of ordinary skill in the art would have been motivated to do this because tris(2-carboxyethyl)phosphine is especially stable over DTT, particularly with out the presence of a metal chelates. Stability is critical for any drug for storage, administration, and manufacture. The fact that an additional ingredient is not required for stability reduces costs, increases storage time, and the duration of use of the drug to be administered.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Response to Arguments

14. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Claims 35-41 have been cancelled. The rejection is moot.

15. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for *every* coronary syndrome and condition, restenosis, asthma, or rectal spasm.

Claims 35-41 have been cancelled the rejection is moot.

Applicant's arguments see pages 5-6 filed 01/09/2008 have been fully considered but they are not persuasive. Applicant's arguments on the issue of enablement have been addressed in the action above.

16. Claims 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For clarification, the rejection was on Page 7, paragraph 7 of the office action on August 14, 2007.

The claims are indefinite as to the expression of "treating a patient in need of nitroglycerin therapy", "mitochondria selective" dithiol", and "reductant capable of activating mtALDH". Claims 35-41 have been cancelled the rejection is moot.

17. Applicant's arguments see page 7 filed 01/09/2008 have been fully considered but they are not persuasive. Applicant's arguments of Weischer et al. are centered on administration of the DHLA to a patient who has become nitroglycerin tolerant and the properties of DHLA. The issues have been addressed in the action above.

18. Applicant's arguments with respect to Murphy, Laursen have been considered but are moot in view of the new grounds of rejection in the action above.

Conclusion

19. Claims 75-83 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GiGi Huang whose telephone number is (571) 272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH

Zohreh Fay (Primary Examiner)